Uterine artery pulsatility index at 30–34 weeks' gestation in the prediction of adverse perinatal outcome

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Running head: Third-trimester fetal Doppler in screening for adverse perinatal outcome

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Abstract

Objective: To investigate the potential value of uterine artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome.

Methods: Screening study in 30,780 singleton pregnancies at 30-34 weeks. Uterine artery pulsatility index (PI) was measured and the values were converted to multiples of the median (MoM) after adjustment from variables in maternal characteristics and medical history that affect the measurements. Multivariable logistic regression analysis was used to determine if uterine artery PI had a significant additional contribution to maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The detection rate (DR) and false positive rate (FPR) of screening by uterine artery PI were estimated for stillbirth, cesarean section for fetal distress, umbilical arterial cord blood pH <7.0 or umbilical venous pH <7.1 and Apgar score <7 at 5 minutes.

Results: The incidence of adverse perinatal outcome was higher in small for gestational age (SGA) than in non-SGA fetuses, but the majority of cases for each adverse outcome were in the non-SGA group, including about 70% of stillbirths and more than 80% of cases of cesarean section for fetal distress, low cord blood pH and low Apgar score. The performance of uterine artery PI >95th percentile in screening for each adverse outcome was poor with DR of 6-16% and FPR of 5-6%. The DR of high uterine artery PI for adverse outcome was higher in the SGA than non-SGA groups, including 24% vs. 13% for stillbirth, 15% vs. 5% for cesarean section for fetal distress, 22% vs. 9% for low cord blood pH and 20% vs. 3% for low Apgar score.

Conclusion: High uterine artery PI at 30-34 weeks' gestation may be useful in the prediction of adverse perinatal outcome in pregnancies with SGA fetuses, but not in those with non-SGA fetuses.

Introduction

Impaired placentation, reflected in increased impedance to flow in the uterine arteries during the first-, second- and third-trimester of pregnancy, is associated with subsequent development of preeclampsia (PE) and delivery of small for gestational age (SGA) neonates [1-7]. There is also evidence that in pregnancies with SGA fetuses or PE persistence of high impedance to flow in the uterine arteries during the third-trimester is associated with increased risk of adverse perinatal events, including stillbirth, cesarean section for fetal distress and low cord blood pH [8-13].

A screening study at 30-34 weeks' gestation, involving more than 30,000 singleton pregnancies, reported that the incidence of adverse perinatal outcome is higher in SGA than in non-SGA fetuses, but the majority of cases for each adverse event are in the non-SGA group, including about 70% of stillbirths and more than 80% of cases of cesarean section for fetal distress, low cord blood pH and low 5 minute Apgar score [14]. This is analogous to screening for Down syndrome where the risk in women aged $\geq$35 years is substantially higher than in younger women but the overall contribution of the latter group is more than twice as high as that of the older age group. On the assumption that adverse outcome is the consequence of impaired placentation reflected in high uterine artery pulsatility index (PI) rather than just small fetal size, it could be argued that prenatal care should focus not only in pregnancies with SGA fetuses but also in those with high uterine artery PI.

The objective of this screening study is to investigate the potential value of uterine artery PI at 30-34 weeks' gestation in the prediction of adverse perinatal outcome by examining the relationship between uterine artery PI and the rates of PE, birth of SGA neonates, stillbirth, cesarean section for fetal distress, umbilical arterial cord blood pH $\leq$7.0 or umbilical venous blood pH $\leq$7.1 and Apgar score <7 at 5 minutes.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, University College London Hospital, London and Medway Maritime Hospital, Kent, between May 2011 and August 2014. This visit, which was held at 30^{+0}-34^{+6} weeks' gestation, included recording of maternal characteristics and medical history, estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks [15,16]. Transabdominal color flow mapping was used to visualize the left and right uterine arteries at the apparent crossover with the external iliac arteries [17]. Pulsed-wave Doppler was then used to obtain waveforms and when three similar consecutive waveforms were obtained the PI was measured, and the mean PI of the two vessels was calculated.

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital.

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous, use of ovulation drugs or *in vitro* fertilization), cigarette smoking during pregnancy (yes or no), medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic

lupus erythematosus (SLE) or anti-phospholipid syndrome (APS) and parity (parous or nulliparous if no previous pregnancies at ≥ 24 weeks). Maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were stillbirth, cesarean section for fetal distress in labor, umbilical arterial cord blood pH ≤7.0 or venous blood pH ≤7.1 and Apgar score <7 at 5 minutes. The newborn was considered to be SGA if the birth weight was less than the 10th percentile after correction for gestational age at delivery [18]. The birth weight Z-score was also derived from the normal range for gestational age [18]. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [19].

Statistical analysis

Comparison between the outcome groups was by χ2-test or Fisher's exact test for categorical variables and Mann Whitney-U test for continuous variables. Categorical data are presented as n (%) and continuous data as median and interquartile range (IQR).

The measured uterine artery PI was expressed as multiple of the median (MoM) after adjustment for variables from maternal characteristics and medical history that affect this measurement [20]. The association between $\log_{10}$ MoM uterine artery PI and birth weight Z-score in each of the adverse outcome groups and those without the adverse outcome was examined in scatterplots. Univariable and multivariable logistic regression analysis was used to determine if $\log_{10}$ MoM uterine artery PI had a significant additional contribution to maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The detection rate (DR) and false positive rate (FPR) of screening by uterine artery PI were estimated for each adverse outcome.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) was used for the data analyses.

Results

Study population

During the study period, we prospectively examined and measured uterine artery PI in 31,804 singleton pregnancies. We excluded 206 (0.6%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 1,337 (4.2%) for no follow-up. The study population comprised of 30,261 pregnancies and included 30,181 with live births and 80 with stillbirths.

The characteristics of the study population and the various subgroups according to outcome are given in Table 1.

Uterine artery PI in pregnancies with PE and those delivering SGA neonates

Preeclampsia developed in 661 (2.2%) of the 30,261 pregnancies, including 152 (0.5%) that delivered at <37 and 509 (1.7%) at ≥37 weeks' gestaion. The median uterine artery PI MoM was significantly higher in both the preterm-PE and term-PE groups than in the non-PE group (Table 2). Delivery of SGA neonates in the absence of PE occurred in 3,213 (10.6%) pregnancies, including 249 (0.8%) at <37 and 2,964 (9.8%) at ≥37 weeks' gestation. The

median uterine artery PI MoM was significantly higher in both the preterm-SGA and term-SGA groups than in the non-SGA group (Table 2).

Uterine artery PI in stillbirth from SGA and non-SGA pregnancies

In the study population there were 80 stillbirths, including 73 antepartum and seven intrapartum. The birth weight was <10th percentile in 25 (31.3%) of the cases. The uterine artery PI was >95th percentile in 6 of the 25 (24.0%) stillbirths with birth weight <10th percentile and 7 of the 55 (12.7%) with birth weight ≥10th percentile. The median uterine artery PI MoM was significantly higher in pregnancies with stillbirth than livebirth, in both the SGA and non-SGA groups (Table 2).

Uterine artery PI in cesarean section for fetal distress from SGA and non-SGA pregnancies

In the 30,181 pregnancies with live births, there were 22,442 with vaginal delivery following spontaneous or induced labor, 3,612 with elective cesarean section for a variety of indications and 4,127 with cesarean section following spontaneous or induced labor; in the latter group the indication for cesarean section was fetal distress in 1,881 cases. In the elective cesarean section group (n=3,612) there were a variety of indications, including breech or transverse lie (n=806), placenta previa (n=171), previous cesarean section, traumatic birth or maternal request (n=2,268), maternal medical disorder (n=214) and fetal compromise diagnosed by abnormal Doppler findings or fetal heart rate patterns (n=153).

In the non-SGA group delivering vaginally the median uterine artery PI was 0.98 MoM and the values were above the 95th percentile in 4.3% (860/19,976) cases. In the 3,612 pregnancies with elective cesarean section the median uterine artery PI (0.98 MoM) was not significantly different from the non-SGA group with vaginal delivery. However, in the subgroup of 153 cases of elective cesarean section for abnormal fetal heart rate patterns or fetal Doppler indices in SGA fetuses, the median uterine artery PI MoM (1.48 MoM) was increased and the values were above the 95th percentile in 71 (46.4%) cases.

In this section we compare the outcome of the 22,442 pregnancies with vaginal delivery and the 1,881 with cesarean section for fetal distress during labor. The birth weight was <10th percentile in 348 (18.5%) of the cases of cesarean section for fetal distress. In the cases requiring cesarean section for fetal distress, the uterine artery PI was >95th percentile in 53 of the 348 (15.2%) cases in the SGA group and in 76 of the 1,533 (5.0%) in the non-SGA group. The median uterine artery PI was significantly higher in those with cesarean section than vaginal delivery in the SGA group (p=0.004), but not in the non-SGA group (p=0.796) (Table 2).

Uterine artery PI in low cord blood pH from SGA and non-SGA pregnancies

In the 30,181 pregnancies with live births, the umbilical arterial and venous cord blood pH was recorded in 9,222 and 12,559 cases, respectively. The umbilical arterial cord blood pH was ≤7.0 in 201 (2.2%) cases and the umbilical venous blood pH was ≤7.1 in 194 (1.5%) cases; low blood pH in either vessel was observed in 253 (2.0%) cases.

The birth weight was <10th percentile in 37 (14.6%) of the cases with low cord blood pH. The uterine artery PI was >95th percentile in 8 of the 37 (21.6%) cases with low cord blood pH and birth weight <10th percentile and 19 of the 216 (8.8%) with birth weight ≥10th percentile. There was no significant difference in the median uterine artery PI MoM between those with low cord blood pH and those with normal pH, in either the SGA or the non-SGA groups (Table 2).

Uterine artery PI in low Apgar score from SGA and non-SGA pregnancies

In the 30,181 pregnancies with live births, the Apgar score at 5 minutes was recorded in 24,552 cases and it was <7 in 251 (1.0%) cases. The birth weight was <10^{th} percentile in 45 (17.9%) of the cases with Apgar score <7. The uterine artery PI was >95^{th} percentile in 9 of the 45 (20.0%) cases with Apgar score <7 and birth weight <10^{th} percentile and 7 of the 206 (3.4%) with birth weight ≥10^{th} percentile. There was no significant difference in the median uterine artery PI MoM between those with Apgar score <7 and those with score of ≥7, in either the SGA or the non-SGA groups (Table 2).

Prediction of stillbirth

The results of univariable and multivariable regression analysis for the prediction of stillbirth are given in sTable 1. Multivariable regression analysis demonstrated that significant contribution to prediction of stillbirth was provided by maternal weight, Afro-Caribbean racial origin, birth weight Z-score and $\log_{10}$ MoM value of uterine artery PI (R^2=0.122, p<0.0001).

The relationship between $\log_{10}$ MoM uterine artery PI and birth weight Z-score in stillbirths and live births is shown in Figure 1. The performance of screening of high uterine artery PI for stillbirth is shown in Table 3. The DR and FPR were 24.0% and 12.7% for the SGA group and 12.7% and 4.5% for the non-SGA group.

Prediction of cesarean section for fetal distress in labor

The results of univariable and multivariable regression analysis for the prediction of fetal distress leading to cesarean section are given in sTable 2. Multivariable regression analysis demonstrated that significant contribution to prediction of fetal distress was provided by maternal age, weight, height, Afro-Caribbean racial origin, nulliparity, gestational diabetes in the current pregnancy, prelabor spontaneous rupture of membranes, induction of labor and $\log_{10}$ MoM value of uterine artery PI (R^2=0.148, p<0.0001).

The relationship between $\log_{10}$ MoM uterine artery PI and birth weight Z-score in the group of cesarean section for fetal distress and those with vaginal delivery is shown in Figure 2. The performance of screening of high uterine artery PI for fetal distress in labor leading to cesarean section is shown in Table 3. The DR and FPR were 15.2% and 9.6% for the SGA group and 5.0% and 4.3% for the non-SGA group.

Prediction of low cord blood pH

The results of univariable and multivariable regression analysis for the prediction of low cord blood pH are given in sTable 3. Multivariable regression analysis demonstrated that significant contribution to prediction of umbilical arterial cord blood pH ≤7.0 or venous blood pH ≤7.1 was provided by maternal weight, height, East Asian racial origin, gestational diabetes mellitus during the current pregnancy, prelabor spontaneous rupture of membranes, onset of labour and method of delivery, but not $\log_{10}$ MoM uterine artery PI (adjusted R^2=0.027, p<0.0001).

The relationship between $\log_{10}$ MoM uterine artery PI and birth weight Z-score in those with low and normal cord blood pH are shown in Figure 3. The performance of screening of high uterine artery PI for low cord blood pH is shown in Table 3. The DR and FPR were 21.6 % and 15.1% for the SGA group and 8.8% and 4.7% for the non-SGA group.

Prediction of low Apgar score

The results of univariable and multivariable regression analysis for the prediction of 5 minute Apgar <7 are given in sTable 4. Multivariable regression analysis demonstrated that significant contribution to prediction of Apgar <7 was provided by maternal height, Afro-Caribbean racial origin, history of SLE or APS and onset of labor and method of delivery, but not $\log_{10}$ MoM uterine artery PI (adjusted R^2=0.040, p<0.0001).

The relationship between uterine artery PI MoM and birth weight Z-score in those with Apgar score <7 and ≥7 is shown in Figure 4. The performance of screening of high uterine artery PI for 5 minute Apgar <7 is shown in Table 3. The DR and FPR were 20.0% and 12.9% for the SGA group and 3.4% and 4.6% for the non-SGA group.

Discussion

Main findings of the study

The findings of this study demonstrate that high uterine artery PI at 30-34 weeks' gestation is associated with subsequent development of PE, delivery of SGA neonates and stillbirth. In SGA, but not in non-SGA fetuses, high uterine artery PI is also associated with fetal distress in labor requiring cesarean section, low cord blood pH and low 5 minute Apgar score.

The rationale for the study was that, if adverse outcome is the consequence of impaired placentation, prenatal care should be directed at identifying and monitoring pregnancies with high uterine artery PI rather than only those with small fetuses. The finding confirm that although the incidence of adverse perinatal outcome is higher in SGA than in non-SGA fetuses, the majority of cases for each adverse outcome are in the AGA group, including about 70% of stillbirths and more than 80% of cases of cesarean section for fetal distress, low cord blood pH and low 5 minute Apgar score.

Measurement of uterine artery PI contributed significantly, in addition to maternal characteristics, medical history and obstetric factors, in the prediction of stillbirth and fetal distress in labor leading to cesarean section. However, the performance of high uterine artery PI in screening for each adverse outcome was poor with DR of 6-16% and FPR of 5-6%. The performance of screening for adverse outcome was higher in the SGA than non-SGA pregnancies; the DR for stillbirth was about 24% vs. 13% and the respective values for cesarean section for fetal distress were 15% vs. 5%, for low cord blood pH were 22% vs. 9% and for low Apgar score were 20% vs. 3%.

Strengths and limitations of the study

The strengths of this third-trimester screening study are firstly, examination of a large population of pregnant women attending for routine care at a gestational age range which is widely used for the assessment of fetal growth and wellbeing, secondly, use of a specific methodology and appropriately trained doctors to measure uterine artery PI and estimate the MoM value after adjustment for factors that affect the measurements, and thirdly, use of a wide range of well accepted indicators of adverse perinatal outcome.

The main limitation of the study is that the results of the 30-34 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions on further monitoring and delivery for the cases of suspected SGA and those with abnormal Doppler findings. Consequently, the performance of screening by uterine artery PI would have been negatively biased. For example, SGA fetuses with abnormal fetal heart rate patterns or fetal Doppler indices were delivered by elective cesarean section and therefore the performance

of uterine artery PI in the prediction of cesarean section for fetal distress in labor would have been underestimated. Similarly, some stillbirths and cases of asphyxia at birth, reflected in low cord blood pH and low Apgar score, could have been avoided. In our study there were 71 pregnancies with SGA fetuses and high uterine artery PI that were delivered by elective cesarean section because of abnormal fetal heart rate patterns or fetal Doppler indices and this number is not negligible by comparison with the number of pregnancies with SGA fetuses and high uterine artery PI that resulted in stillbirth (n=6), cesarean section for fetal distress (n=53), low arterial blood pH (n=6), low venous blood pH (n=10) or low Apgar score (n=9).

Comparison with findings from previous studies

Previous studies in a small number of pregnancies with SGA fetuses reported that high impedance to flow in the uterine arteries during the third-trimester is associated with increased risk of adverse perinatal events, including stillbirth, cesarean section for fetal distress and low cord blood pH [8,9,11-13]. Our study, evaluated uterine artery PI as part of routine screening for adverse perinatal outcome in all pregnant women at 30-34 weeks' gestation. Our results confirm those of the previous studies concerning SGA fetuses and in addition they demonstrate that, in general, high uterine PI is not useful in the prediction of adverse perinatal outcome in pregnancies with non-SGA fetuses.

This study has shown that high uterine artery PI at 30-34 weeks predicts about 50% of cases that subsequently deliver with preterm-PE and 33% of preterm-SGA in the absence of PE; the DR for term-PE and term-SGA was 13% and 9%, respectively. In previous third-trimester screening studies we combined maternal characteristics and medical history with uterine artery PI, mean arterial pressure, serum placental growth factor and serum soluble fms-like tyrosine kinase-1 and such combined screening predicted 99% of preterm-PE and 75% of term-PE [21]. Similarly, combined screening, with maternal characteristics and medical history with estimated fetal weight, uterine artery PI, mean arterial pressure and serum placental growth factor, predicted 89% of preterm-SGA and 57% of term-SGA [22].

Implications for clinical practice

Measurement of uterine artery PI at 30-34 weeks' gestation should be an integral part of combined screening with maternal factors and biomarkers which predicts most cases of SGA and / or PE [21,22]. Such screening will identify the high-risk group in need of close monitoring for fetal growth and wellbeing to define the best time and mode of delivery. Within the SGA group, high uterine artery PI identifies a subgroup at increased risk of adverse perinatal events. In the absence of SGA, uterine artery PI is not useful in predicting fetal distress in labor, low cord blood pH or low Apgar score.

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Figure legends

Figure 1. Relationship between $\log_{10}$ uterine artery pulsatility index (PI) multiple of the median (MoM) and birth weight Z-score in stillbirths (red dots) and live births (black dots). The vertical red line corresponds to the 10th percentile for birth weight and the horizontal red line corresponds to the 95th percentile for the uterine artery PI.

Figure 2. Relationship between $\log_{10}$ uterine artery pulsatility index (PI) multiple of the median (MoM) and birth weight Z-score in pregnancies delivering by cesarean section for fetal distress (red dots) and those delivering vaginally (black dots). The vertical red line corresponds to the 10th percentile for birth weight and the horizontal red line corresponds to the 95th percentile for the uterine artery PI.

Figure 3. Relationship between $\log_{10}$ uterine artery pulsatility index (PI) multiple of the median (MoM) and birth weight Z-score in those with arterial cord blood pH $\leq$7.0 or venous blood pH $\leq$7.1 (red dots) and pH >7.0 (black dots). The vertical red line corresponds to the 10th percentile for birth weight and the horizontal red line corresponds to the 95th percentile for the uterine artery PI.

Figure 4. Relationship between $\log_{10}$ uterine artery pulsatility index (PI) multiple of the median (MoM) and birth weight Z-score in those with a 5 minute Apgar score <7 (red dots) and Apgar $\geq$7 (black dots). The vertical red line corresponds to the 10th percentile for birth weight and the horizontal red line corresponds to the 95th percentile for the uterine artery PI.

Table 1. Maternal and pregnancy characteristics of the study population and subgroups of stillbirth, fetal distress in labor leading to cesarean section, low umbilical arterial or venous cord blood pH and low 5 minute Apgar score. In each group the data are compared to the cohort without the outcome measure.

Variable	Population (n=30,261)	Stillbirth (n=80)	Fetal distress (n=1,881)	Low cord blood pH (n=253)	Low Apgar score (n=251)
GA at assessment (w)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	32.3 (32.0-32.8)**	32.3 (32.0-32.9)
Delivery interval (w)	7.4 (6.3-8.4)	6.3 (4.3-8.3)**	8.0 (6.6-9.0)**	7.3 (5.9-8.6)	7.6 (5.9-8.6)
Maternal characteristics					
Maternal age (y)	31.3 (26.8-35.0)	30.0 (25.2-35.9)	31.1 (26.7-35.4)**	30.4 (26.4-34.6)	30.7 (26.1-34.3)
Maternal weight (Kg)	75.5 (67.8-85.6)	82.5 (70.0-94.5)**	78.2 (69.5-89.9)**	78.0 (71.0-85.9)	76.0 (68.0-87.0)
Maternal height (m)	1.65 (1.60-1.69)	1.65 (1.62-1.68)	1.63 (1.58-1.68)**	1.63 (1.58-1.68)**	1.63 (1.59-1.67)**
Cigarette smoker	2,741 (9.1)	11 (13.8)	159 (8.5)	28 (11.1)	22 (8.8)
Racial origin					
Caucasian	21,281 (70.3)	47 (58.8)	1,175 (62.5)**	169 (66.8)	145 (57.8)**
Afro-Caribbean	5,582 (18.4)	26 (32.5)**	489 (26.0)**	52 (20.6)	84 (33.5)**
South Asian	1,754 (5.8)	5 (6.3)	126 (6.7)	23 (9.1)*	15 (6.0)
East Asian	943 (3.1)	2 (2.5)	56 (3.0)	2 (0.8)*	2 (0.8)*
Mixed	701 (2.3)	0 (0.0)	35 (1.9)	7 (2.8)	5 (2.0)
Conception					
Spontaneous	29,117 (96.2)	76 (95.0)	1,798 (95.6)	247 (97.6)	244 (97.2)
Assisted conception	1,144 (3.8)	4 (5.0)	83 (4.4)**	6 (2.4)	7 (2.8)
Medical disorder					
Chronic hypertension	404 (1.3)	2 (2.5)	29 (1.5)*	4 (1.6)	4 (1.6)
SLE / APS	58 (0.2)	0 (0.0)	7 (0.4)	0 (0.0)	3 (1.2)**
Diabetes mellitus	281 (0.9)	0 (0.0)	24 (1.3)**	2 (0.8)	4 (1.6)
Obstetric history					
Parous	15,076 (49.8)	38 (47.5)	504 (26.8)	108 (42.7)	103 (41.0)
Nulliparous	15,185 (50.2)	42 (52.5)	1,377 (73.2)**	145 (57.3)	148 (59.0)
Pregnancy complication					
Preeclampsia	661 (2.2)	3 (3.8)	90 (4.8)**	10 (4.0)	11 (4.4)*
Gestational diabetes	739 (2.4)	2 (2.5)	57 (3.0)**	16 (6.3)	10 (4.0)
Obstetric cholestasis	146 (0.5)	0 (0.0)	14 (0.7)	1 (0.4)	0 (0.0)
SROM	1,580 (5.2)	1 (1.3)	209 (11.1)**	10 (4.0)*	11 (4.4)
Onset of labor and mode of delivery					
Spontaneous labor, VD	19,374 (64.0)	24 (30.0)	-	124 (49.0)	111 (44.2)**
Spontaneous labor, CS	2,909 (9.6)	-	-	57 (22.2)**	50 (19.9)**
Induced labor, VD	3,143 (10.4)	51 (63.7)	-	26 (10.3)	31 (12.4)
Induced labor, CS	1,218 (4.0)	-	639 (34.0)**	24 (9.5)	32 (12.7)**
Elective CS	3,617 (12.0)	5 (6.3)	-	22 (8.7)*	27 (10.8)
Outcome					
GA at delivery (w)	40.0 (39.0-40.9)	38.9 (37.1-40.8)**	40.5 (39.3-41.4)**	40.0 (38.7-41.0)	40.0 (38.6-41.1)

Birth weight (g)	3390 (3064-3710)	3000 (2637-3554)**	3352 (3016-3704)**	3434 (2952-3757)	3370 (2935-3370)
Birth weight (percentile)	46.5 (22.3-72.7)	28.0 (7.0-74.6)**	37.9 (14.5-68.6)**	48.8 (16.7-75.0)	46.7 (14.7-73.9)

SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome; SROM = Spontaneous rupture of membranes; VD = vaginal delivery; CS = cesarean section; GA = gestational age

* = $p<0.05$; ** = $p<0.01$

Table 2. Uterine artery pulsatility index and adverse perinatal outcome.

Outcome	Uterine artery PI	
	Median (IQR)	n (%) > 95th centile
PE at <37 weeks	1.60 (1.19-2.00)***	77/152 (50.7)***
PE at ≥37 weeks	1.06 (0.87-1.35)***	64/509 (12.6)***
No PE (reference)	0.99 (0.85-1.17)	1,517/29,600 (5.1)
SGA in the absence of PE at <37 weeks	1.27 (0.98-1.70)***	81/249 (32.5)***
SGA in the absence of PE at ≥37 weeks	1.05 (0.89-1.28)***	275/2,964 (9.3)***
Non-SGA in the absence of PE (reference)	0.98 (0.84-1.16)	1,161/26,387 (4.4)
SGA stillbirth	1.30 (1.06-1.58)***	6/25 (24.0)**
SGA livebirth	1.07 (0.90-1.34)***	428/3,379 (12.7)***
Non-SGA stillbirth	1.09 (0.91-1.31)**	7/55 (12.7)*
Non-SGA livebirth (reference)	0.99 (0.84-1.16)	1,217/26,802 (4.5)
SGA cesarean section for fetal distress	1.10 (0.91-1.41)***	53/348 (15.2)***
SGA vaginal delivery	1.05 (0.89-1.28)***	236/2,466 (9.6)***
Non-SGA cesarean section for fetal distress	0.98 (0.84-1.15)	76/1,533 (5.0)
Non-SGA vaginal delivery (reference)	0.98 (0.84-1.15)	860/19,976 (4.3)
SGA arterial blood pH <7.0	1.11 (0.99-1.54)**	6/25 (24.0)**
SGA arterial blood pH ≥7.0	1.11 (0.91-1.38)***	174/1,108 (15.7)***
Non-SGA arterial blood pH <7.0	1.01 (0.84-1.19)	15/176 (8.5)
Non-SGA arterial blood pH ≥7.0 (reference)	0.99 (0.85-1.16)	396/7,913 (5.0)
SGA venous blood pH <7.1	1.18 (0.94-1.63)**	10/37 (27.0)***
SGA venous blood pH ≥7.1	1.10 (0.90-1.37)***	220/1,471 (15.0)***
Non-SGA venous blood pH <7.1	1.02 (0.85-1.21)	14/157 (8.9)*
Non-SGA venous blood pH ≥7.1 (reference)	0.98 (0.85-1.16)	514/10,894 (4.7)
SGA Apgar score <7 at 5 minutes	1.09 (0.89-1.46)**	9/45 (20.0)***
SGA Apgar score ≥7 at 5 minutes	1.08 (0.90-1.34)***	354/2,743 (12.9)***
Non-SGA Apgar score <7 at 5 minutes	0.96 (0.82-1.12)	7/206 (3.4)
Non-SGA Apgar score ≥7 at 5 minutes (reference)	0.98 (0.84-1.16)	998/21,558 (4.6)

PE = preeclampsia; SGA = small for gestational age with birth weight <10th percentile; Non-SGA = birth weight ≥10th percentile
Significance value *p<0.05; ** p<0.01; ***p<0.0001

Table 3. Performance of screening of uterine artery pulsatility index > 95th percentile in the prediction of adverse perinatal outcome.

Adverse event	BW centile	DR, n/n (%)	FPR, n/n (%)
Stillbirth (n=80)	≤ 10th centile	6/25 (24.0)	428/3379 (12.7)
	> 10th centile	7/55 (12.7)	1217/26802 (4.5)
	Total	13/80 (16.3)	1645/30181 (5.5)
Fetal distress (n=1881)	≤ 10th centile	53/348 (15.2)	236/2,466 (9.6)
	> 10th centile	76/1,533 (5.0)	860/19,976 (4.3)
	Total	129/1,881 (6.9)	1,096/22,442 (4.9)
Arterial pH ≤7.0 or venous pH ≤7.1 (n=253)	≤ 10th centile	8/37 (21.6)	222/1471 (15.1)
	> 10th centile	19/216 (8.8)	509/10,835 (4.7)
	Total	27/253 (10.7)	731/123,306 (5.9)
5-min Apgar < 7.0 (n=251)	≤ 10th centile	9/45 (20.0)	354/2,743 (12.9)
	> 10th centile	7/206 (3.4)	998/21,558 (4.6)
	Total	16/251 (6.4)	1,352/24,301 (5.6)

BW = birth weight; DR = detection rate; FPR = false positive rate

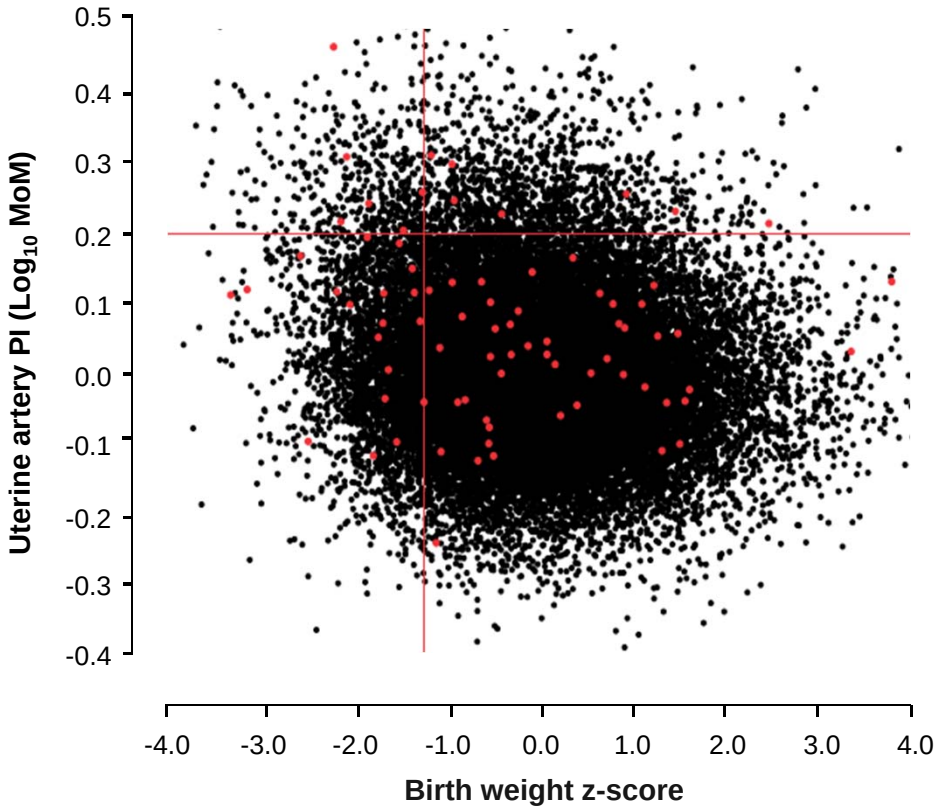

Figure 1

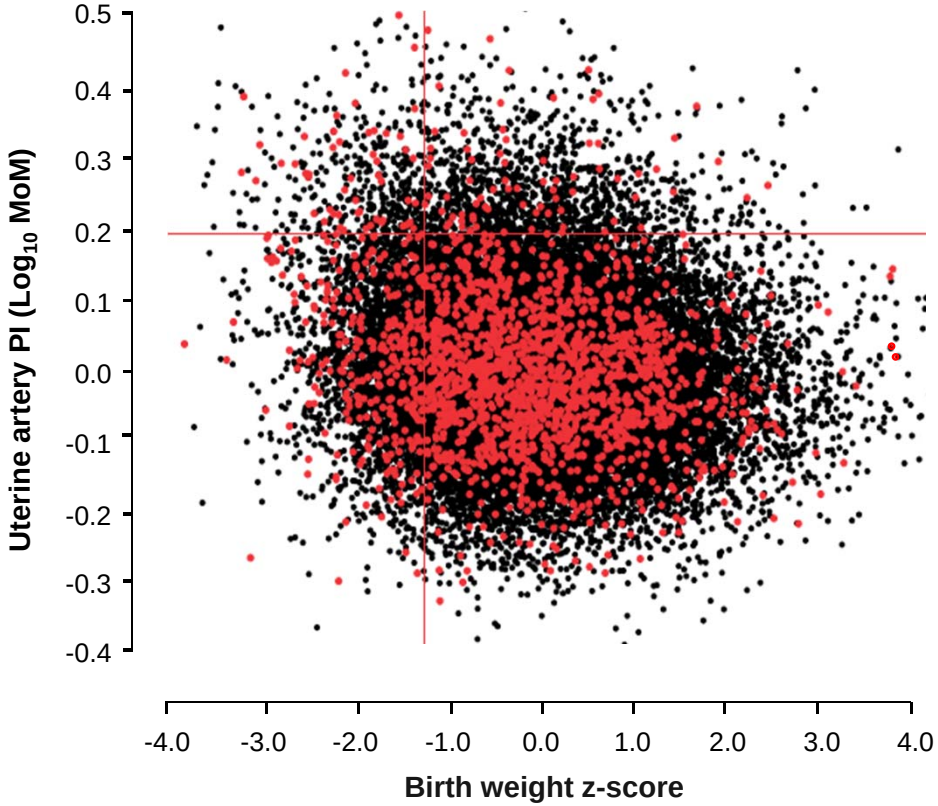

Figure 2

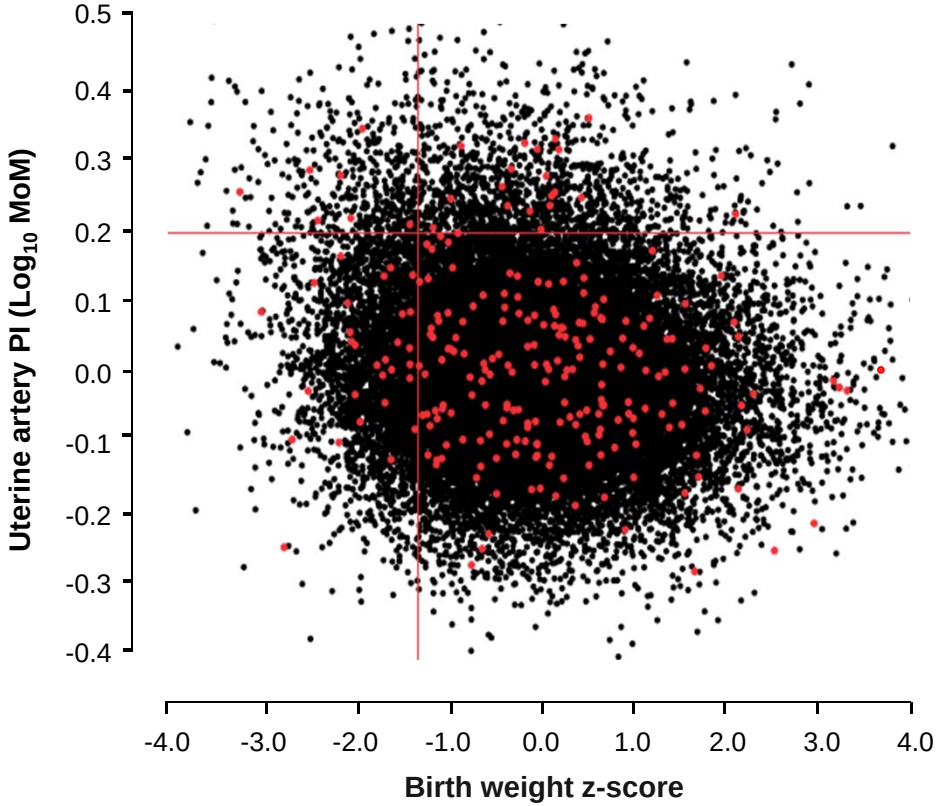

Figure 3

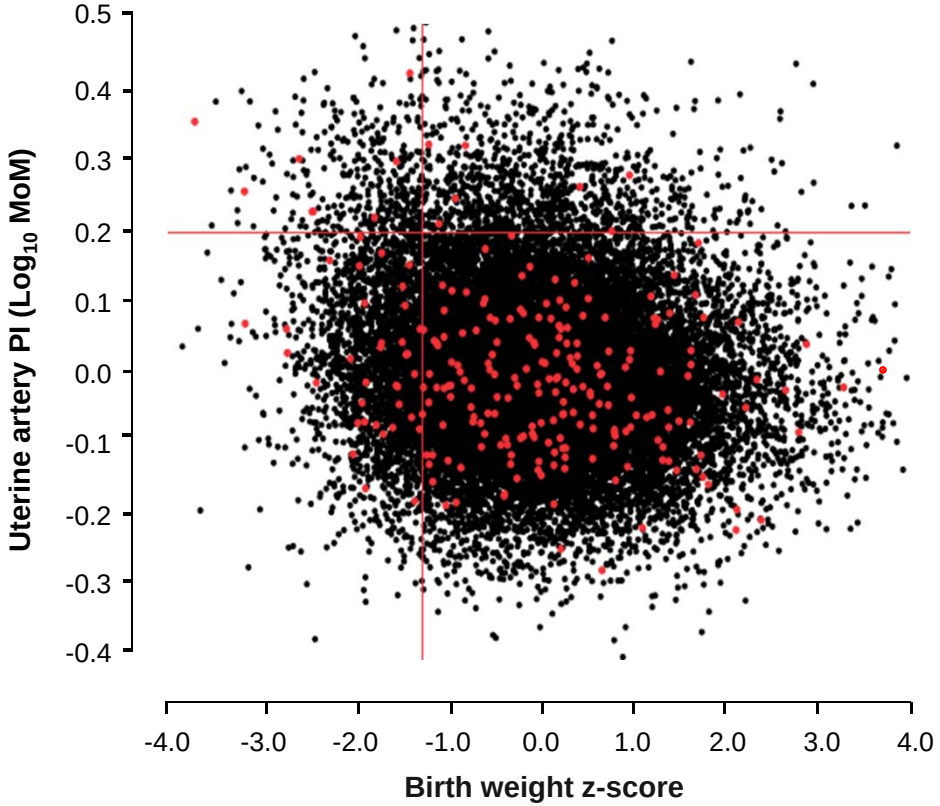

Figure 4